

WHAT IS CLAIMED IS:

1. An antibody that immunospecifically binds to BLYS comprising a first amino acid sequence at least 95% identical to an second amino acid sequence selected from the group consisting of:

(a) an amino acid sequence comprising the amino acid sequence of a VHCDR of any one of the scFvs of SEQ ID NOS:1 through 2128; and

(b) an amino acid sequence comprising the amino acid sequence of a VLCDR of any one of the scFvs of SEQ ID NOS:1 through 2128.

2. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VHCDR3 of any one of the scFvs of SEQ ID NOS:2129 through 3227.

3. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VH domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

4. The antibody of claim 3 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1 through 1562.

5. The antibody of claim 4 in which said antibody immunospecifically binds to both the soluble form and membrane-bound form of BLYS.

6. The antibody of claim 4 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1 through 46 and 321 through 329.

7. The antibody of claim 6 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 2, 9, and 327.

8. The antibody of claim 4 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 834 through 872.

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9. The antibody of claim 3 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1563 through 1880.

10. The antibody of claim 9 in which, and in which said antibody immunospecifically binds to the soluble form of BLYS.

11. The antibody of claim 9 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1563 through 1569.

12. The antibody of claim 9 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1570 through 1595.

13. The antibody of claim 3 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1881 through 2128.

14. The antibody of claim 13 in which said antibody immunospecifically binds to the membrane-bound form of BLYS.

15. The antibody of claim 13 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1881 through 1885.

16. The antibody of claim 13 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1886 through 1908.

17. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS: 1 through 2128.

18. The antibody of claim 17 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1 through 1562.

19. The antibody of claim 18 in which said antibody immunospecifically binds to both the soluble form and membrane-bound form of BLYS.

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20. The antibody of claim 18 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1 through 46 and 321 through 329.

21. The antibody of claim 20 in which said VL domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 2, 9, and 327.

22. The antibody of claim 18 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 834 through 872.

23. The antibody of claim 17 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1563 through 1880.

24. The antibody of claim 23 said antibody immunospecifically binds to the soluble form of BLYS.

25. The antibody of claim 23 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1563 through 1569.

26. The antibody of claim 23 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1570 through 1595.

27. The antibody of claim 17 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1881 through 2128.

28. The antibody of claim 27 in which said antibody immunospecifically binds to the membrane-bound form of BLYS.

29. The antibody of claim 27 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1881 through 1885.

30. The antibody of claim 27 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1886 through 1908.

31. The antibody of claim 3, which also comprises an amino acid sequence at least 95% identical to the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

32. The antibody of claim 31, wherein the VH and VL domains are from the same scFv.

33. The antibody of claim 32, wherein the scFv is the scFv of SEQ ID NO:2.

34. The antibody of claim 32, wherein the scFv is the scFv of SEQ ID NO:9.

35. The antibody of claim 32, wherein the scFv is the scFv of SEQ ID NO:327.

36. The antibody of claim 1 wherein the first amino acid sequence is identical to the second amino acid sequence.

37. The antibody of claim 36 wherein the second amino acid sequence consists of the amino acid sequence of a VH domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

38. The antibody of claim 36 wherein the second amino acid sequence consists of the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

39. The antibody of claim 37 which also comprises an amino acid sequence 100% identical to the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

40. The antibody of claim 39, wherein the scFv is the scFv of SEQ ID NO:2.

41. The antibody of claim 39, wherein the scFv is the scFv of SEQ ID NO:9.

42. The antibody of claim 39, wherein the scFv is the scFv of SEQ ID NO:327.

43. The antibody of claim 1, wherein the BLYS is a BLYS homotrimer.
44. The antibody of claim 43, wherein the individual protein components of the BLYS homotrimer consist of the mature form of BLYS.
45. The antibody of claim 1, wherein the BLYS is a BLYS heterotrimer.
46. The antibody of claim 45, wherein the BLYS heterotrimer comprises at least one BLYS polypeptide and at least one APRIL polypeptide.
47. The antibody of claim 46, wherein the BLYS polypeptide consists of the mature form of BLYS and the APRIL polypeptide consists of the mature form of APRIL.
48. The antibody of claim 1, wherein the antibody is selected from the group consisting of:
 - (a) a whole immunoglobulin molecule;
 - (b) an scFv;
 - (c) a monoclonal antibody;
 - (d) a human antibody;
 - (e) a chimeric antibody;
 - (f) a humanized antibody;
 - (g) a Fab fragment;
 - (h) an Fab' fragment;
 - (i) an F(ab')₂;
 - (j) an Fv; and
 - (k) a disulfide linked Fv.
49. The antibody of claim 3 or 37, which also comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:
 - (a) a human IgM constant domain;
 - (b) a human IgG1 constant domain;
 - (c) a human IgG2 constant domain;
 - (d) a human IgG3 constant domain;

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- (e) a human IgG4 constant domain; and
- (f) a human IgA constant domain.

50. The antibody of claim 17 or 38, which also comprises a light chain immunoglobulin constant domain selected from the group consisting of:

- (a) a human Ig kappa constant domain;
- (b) a human Ig lambda constant domain.

51. The antibody of claim 1, wherein the antibody has a dissociation constant (K_D) selected from the group consisting of:

- (a) a dissociation constant (K_D) between 10^{-7} M and 10^{-8} M;
- (b) a dissociation constant (K_D) between 10^{-8} M and 10^{-9} M;
- (c) a dissociation constant (K_D) between 10^{-9} M and 10^{-10} M;
- (d) a dissociation constant (K_D) between 10^{-10} M and 10^{-11} M;
- (e) a dissociation constant (K_D) between 10^{-11} M and 10^{-12} M; and
- (f) a dissociation constant (K_D) between 10^{-12} M and 10^{-13} M.

52. The antibody of claim 1, wherein the antibody is conjugated to a detectable label.

53. The antibody of claim 52, wherein the detectable label is a radiolabel.

54. The antibody of claim 53, wherein the radiolabel is ^{125}I , ^{131}I , ^{111}In , ^{90}Y , ^{99}Tc , ^{177}Lu , ^{166}Ho , or ^{153}Sm .

55. The antibody of claim 52, wherein the detectable label is an enzyme, a fluorescent label, a luminescent label, or a bioluminescent label.

56. The antibody of claim 1, wherein the antibody is biotinylated.

57. The antibody of claim 1, wherein the antibody is conjugated to a therapeutic or cytotoxic agent.

58. The antibody of claim 57, wherein the therapeutic or cytotoxic agent is selected from the group consisting of:

- (a) an anti-metabolite,
- (b) an alkylating agent;
- (c) an antibiotic;
- (d) a growth factor;
- (e) a cytokine;
- (f) an anti-angiogenic agent;
- (g) an anti-mitotic agent;
- (h) an anthracycline;
- (i) toxin; and
- (j) an apoptotic agent.

59. An antibody of claim 1, that neutralizes BLyS or a fragment thereof.

60. The antibody of claim 59, that diminishes or abolishes the ability of BLyS or a fragment thereof to bind to its receptor.

61. The antibody of claim 60, wherein the receptor is TACI.

62. The antibody of claim 60, wherein the receptor is BCMA.

63. The antibody of claim 59, that diminishes or abolishes the ability of BLyS or a fragment thereof to stimulate B cell proliferation.

64. The antibody of claim 59, that diminishes or abolishes the ability of BLyS or a fragment thereof to stimulate immunoglobulin secretion by B cells.

65. An antibody of claim 1, that enhances the activity of BLyS or a fragment thereof.

66. The antibody of claim 65, that increases the ability of BLyS or a fragment thereof to bind to its receptor.

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67. The antibody of claim 66, wherein the receptor is TACI.

68. The antibody of claim 66, wherein the receptor is BCMA.

69. The antibody of claim 65, that increases the ability of BLyS or a fragment thereof to stimulate B cell proliferation.

70. The antibody of claim 65, that increases the ability of BLyS or a fragment thereof to stimulate immunoglobulin secretion by B cells.

71. The antibody of claim 1 covalently linked to a heterologous polypeptide.

72. The antibody of claim 71, wherein the heterologous polypeptide is human serum albumin.

73. The antibody of claim 1 in a pharmaceutically acceptable carrier.

74. A kit comprising the antibody of claim 1.

sub
a1 } 75. An isolated nucleic acid molecule encoding the antibody of claim 1.

76. A vector comprising the isolated nucleic acid molecule of claim 75.

77. The vector of claim 76 which also comprises a nucleotide sequence which regulates the expression of the antibody encoded by the nucleic acid molecule.

78. A host cell comprising the nucleic acid molecule of claim 77.

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a1 } 79. A cell line engineered to express the antibody of claim 1.

80. An antibody that binds the same epitope as the antibody of claim 1.

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a1 } 81. An antibody that competitively inhibits the binding of the antibody produced by the cell line having ATCC Deposit Number PTA-3239.

82. An antibody that competitively inhibits the binding of the antibody produced by the cell line having ATCC Deposit Number PTA-3240

83. An antibody that competitively inhibits the binding of the antibody produced by the cell line having ATCC Deposit Number PTA-3243.

84. An second antibody that reduces the binding of the antibody of claim 1 by an increment within a percentage range selected from the group consisting of:

- (a) from 50% up to 60%;
- (b) from 60% up to 70%;
- (c) from 70% up to 80%;
- (d) from 80% up to 90%; and
- (e) from 90% up to 100%.

85. An antibody that immunospecifically binds to BLYS, said antibody comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH domain of an scFv comprising an amino acid sequence of any one of SEQ ID NOS: 1 to 2128.

86. An antibody that immunospecifically binds to BLYS, said antibody comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VL domain from an scFv comprising an amino acid sequence of any one of SEQ ID NOS: 1 to 2128.

87. A method for detecting aberrant expression of BLYS protein, comprising:

- (a) assaying the level of BLYS expression in a first biological sample of an individual using one or more antibodies or fragments or variants thereof of claim 1; and
- (b) comparing the level of BLYS assayed in biological sample with a standard level of BLYS expression or level of BLYS in a second, normal biological sample;
- (c) wherein an increase or decrease in the assayed level of BLYS in the first biological sample compared to the standard level of BLYS expression or level of BLYS in a second, normal biological sample, is indicative of aberrant expression.

88. A method for diagnosing a disease or disorder associated with aberrant BLyS expression or activity, comprising:

- (a) administering to a subject an effective amount of a labeled antibody of claim 1 that immunospecifically binds to BLYS;
- (b) waiting for a time interval following the administering for permitting the labeled antibody of claim 1 to preferentially concentrate at sites in the subject where BLYS is expressed;
- (c) determining background level; and
- (d) detecting the labeled antibody of claim 1 in the subject, such that detection of labeled antibody above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of BLYS.

89. A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B₂2 expression or activity, comprising administering to an animal in need thereof, the pharmaceutical composition of claim 73 in an amount effective to treat, prevent or ameliorate the disease or disorder.

90. The method of claim 89, wherein the disease or disorder is cancer.

91. The method of claim 89, wherein the disease or disorder of the immune system.

92. The method of claim 91, wherein the disease or disorder of the immune system is an autoimmune disease or disorder.

93. The method of claim 92, wherein the disease or disorder of the immune system is an autoimmune disease or disorder selected from the group consisting of:

- (a) Systemic Lupus Erythematosus; and
- (b) Rheumatoid Arthritis.

94. The method of claim 91, wherein the disease or disorder of the immune system is an immunodeficiency.

95. The method of claim 92, wherein the disease or disorder of the immune system is an immunodeficiency selected from the group consisting of:

- (a) Common Variable Immunodeficiency (CVID); and
- (b) AIDS.

96. The method of claim 91, wherein the disease or disorder of the immune system is cancer.

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